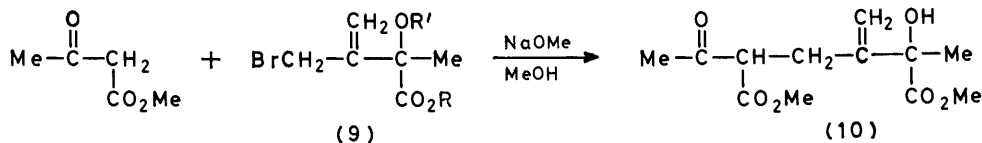
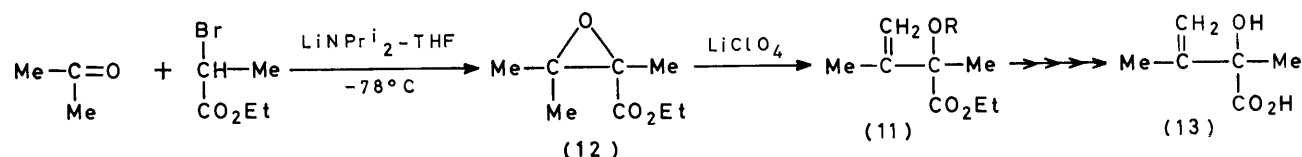


chlorate according to the method of Rickborn *et al.*⁷ The yields in the synthesis of the glycidic ester (12), achieved by the Darzens condensation,⁸ were increased (90%) when lithium di-isopropylamide in tetrahydrofuran (THF)⁹ replaced potassium t-butoxide in t-butyl alcohol.

Although the resolution of the ester (11) was crucial for a successful absolute synthesis of swazinecic acid

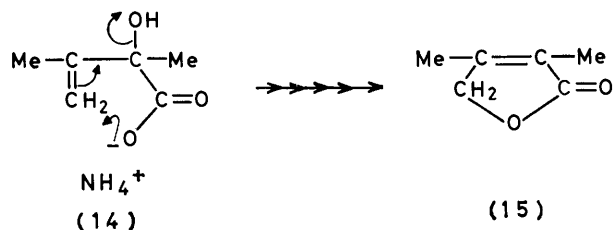


SCHEME 1



SCHEME 2

dilactone, all attempts at such resolution were unsuccessful.¹⁰ Further, all salts of this acid with nitrogenous bases, even that with ammonia, melted over a wide range (160–180°), owing to decomposition near the m.p. with the production of β -methylangelica lactone (15) (Scheme 3) (*cf.* ref. 6). The energetically more



SCHEME 3

favoured $\alpha\beta$ -unsaturated compound (15) was no doubt formed by allylic rearrangement and lactonisation of the salt (14).¹¹

Allylic bromination of the ester (11; R = H) in bright sunlight gave >90% yields of crude product (*cf.*⁶ 46% by using benzoyl peroxide). Although Edwards *et al.*⁶ reported that the product (9; R = Me, R' = H) could be readily distilled (at 55 °C and 0.25 mmHg), in our hands a black viscous residue always resulted even at pressures down to 5×10^{-3} mmHg, and yields of pure (9; R = Et, R' = H) never exceeded 10%. However, this compound was adequately purified by passing it through a short silica gel column with benzene as

⁷ B. C. Hartman and B. Rickborn, *J. Org. Chem.*, 1972, **37**, 943.

⁸ M. S. Newman and B. J. Magarlein, *Org. Reactions*, 1949, **5**, 413.

⁹ R. F. Borch, *Tetrahedron Letters*, 1972, 3761.

¹⁰ F. M. Hauser, M. L. Coleman, R. C. Huffman, and F. I. Carrol, *J. Org. Chem.*, 1974, **39**, 3426.

¹¹ R. H. de Wolfe and W. G. Young, *Chem. Rev.*, 1956, **56**, 753.

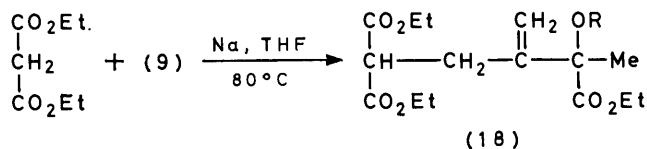
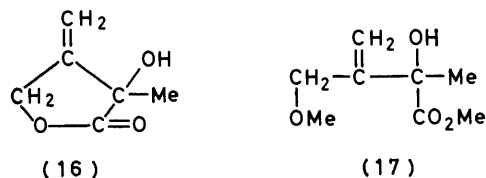
¹² A. Löffler, R. J. Pratt, H. P. Reusch, and A. S. Drieding, *Helv. Chim. Acta*, 1970, **53**, 383.

eluant. It has been reported that allylic bromo-esters show tendencies not only to isomerise but also to lactonise on heating with the loss of an alkyl bromide.¹² The breakdown of (9; R = Et, R' = H) at ambient temperatures gave the lactone (16), which was more readily obtained by treating (9; R = Et, R' = H) with sodium hydroxide.

In the coupling reaction of (9) with diethyl malonate

to form the hexanedioic acid derivative (18) (Scheme 4), tetrahydrofuran or benzene was used as solvent in place of methanol⁶ owing to the tendency of (9) to form the γ -ether (17) by solvolysis.

Because of the acidity of ethyl acetoacetate (pK_a 10.2) Edwards⁶ found it unnecessary to protect the tertiary hydroxy-group in (9; R = Me, R' = H) before coupling. However, with the use of diethyl malonate (pK_a 13.2), protection of the hydroxy-group was essential. Attempted *O*-substitution of such a tertiary hydroxy-group



SCHEME 4

with many protecting groups,¹³ including tetrahydropyranyl^{14,15} and methylthiomethyl,^{16,17} was unsuccessful. However both the *O*-ethoxycarbonyl (75%)^{18,19}

¹³ J. F. W. McOmie, 'Protective Groups in Organic Chemistry,' Plenum Press, London, 1973.

¹⁴ D. N. Robertson, *J. Org. Chem.*, 1960, **25**, 931.

¹⁵ I. Elphimoff-Felkin, *Bull. Soc. chim. France*, 1955, 784.

¹⁶ K. Yamada, K. Kato, H. Nagase, and Y. Hirata, *Tetrahedron Letters*, 1976, 65.

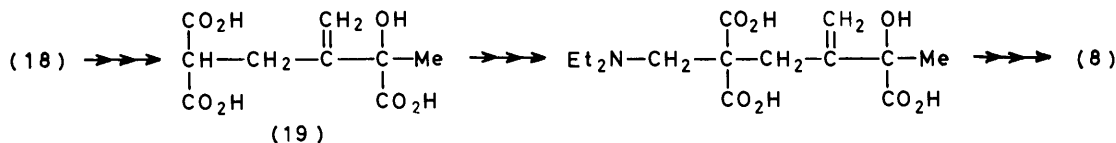
¹⁷ E. J. Corey and M. G. Bock, *Tetrahedron Letters*, 1975, 3269.

¹⁸ L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, 1950, **72**, 5530.

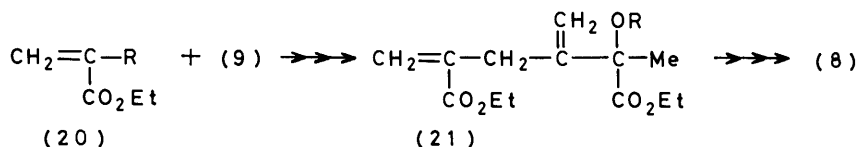
¹⁹ L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero, and T. Utne, *J. Amer. Chem. Soc.*, 1952, **74**, 3309.

and *O*-trimethylsilyl (85%) derivatives of (11) were prepared at 0 °C, by addition of ethyl chloroformate and trimethylsilyl chloride, respectively to (11; R = Na). The usual silylation procedures²⁰ with this silyl chloride or with dimethyl-*t*-butylsilyl chloride²¹ in the presence, or absence, of tertiary amine hydrogen chloride acceptors, or with the more suitable reagent *N*-trimethylsilylacetamide²² were, however, unsuccessful.

The desired coupled product (18; R = CO₂Et) (Scheme 4) was obtained, in 75% yield, by using the ester (9; R = Et, R' = CO₂Et) with sodiomalonate generated with sodium hydride in dry tetrahydrofuran.



SCHEME 5



SCHEME 6

Hydrolysis of (18) produced the triacid (19) which, after stirring with 1 equiv. of a Mannich reagent (prepared from aqueous formaldehyde, diethylamine, and a buffered acetic acid solution^{23,24}) gave the desired compound (8), m.p. 120–121°, in 70% yield (Scheme 5). However, the low overall yield of (8) based on the bromo-derivative (9; R = Et, R' = CO₂Et) (38%) led us to devise a second synthesis of (8).

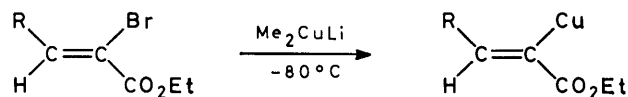
The formation of carbon–carbon bonds by reactions of lithium ester enolates with halides was recently advocated by Rathke *et al.*²⁵ and Cregge *et al.*²⁶ However, since lithium enolates had greater reactivity towards carbonyl groups than organic halides,^{25,27} the enolate (20; R = Li) (Scheme 6) could not be used. By contrast the versatility of the reaction of organocopper reagents with organic halides has been mentioned on several occasions,^{28–31} and in view of their relatively low reactivity with carbonyl groups, especially esters^{32,33} the

formation and reaction of α -ethoxycarbonylvinyl copper (20; R = Cu) was investigated.

One approach to the synthesis of (20; R = Cu) which we considered was the transformation of the lithio-derivative (20; R = Li) *via* metal–metal exchange with copper.³⁴ However all attempts to produce (20; R = Li), through reaction of ethyl α -bromoacrylate with butyl-lithium in the 'Trapp' solution at –115 °C, analogous to that reported for an α -bromo- β -diphenylacrylate³⁵ and an α -bromo- β -phenylacrylate,³⁶ failed and only polymerised adducts resulted.³⁷

Klein and Levene³⁸ have reported that the action of

lithium dimethylcuprate on ethyl 2-bromocinnamate and ethyl 2-bromocrotonate at –80 °C, produced the corresponding α -cuprio-derivatives with retention of configuration (Scheme 7). Our attempts at repeating



SCHEME 7

this reaction with ethyl 2-bromoacrylate yielded only conjugate addition products (ethyl butyrate) in very low yield. Clearly substituents on the β -carbon atom play an important role, through either steric hindrance or charge delocalisation, in reactions of this nature.

The use of the bisethoxycarbonylvinylcuprate (22) proved impossible since its preparation would have involved the reaction of the unattainable ethoxy-carbonylmethyl-lithium (20; R = Li) with copper(I) iodide. Furthermore the large excess of the cuprate

²⁰ A. E. Pierce, 'Silylation of Organic Compounds,' Pierce Chemical Co., Rockford, 1968.

²¹ E. J. Corey and A. Venkateswarki, *J. Amer. Chem. Soc.*, 1972, **94**, 6190.

²² L. Birkofer and A. Ritter, *Angew. Chem. Internat. Edn.*, 1965, **4**, 417.

²³ P. A. Grieco, *Synthesis*, 1975, **2**, 67.

²⁴ J. Martin, P. C. Watts, and F. Johnson, *Chem. Comm.*, 1970, 27.

²⁵ M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, 1971, **93**, 2318.

²⁶ R. J. Cregge, J. L. Herman, C. S. Lee, J. E. Richman, and R. H. Schlessner, *Tetrahedron Letters*, 1973, 2425.

²⁷ M. W. Rathke, *J. Amer. Chem. Soc.*, 1970, **92**, 3222.

²⁸ E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, 1967, **89**, 3911.

²⁹ E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, 1968, **90**, 5615.

³⁰ G. M. Whitesides, W. F. Fischer, jun., J. San Filippo, jun., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, 1969, **91**, 4871.

³¹ E. J. Corey and I. Kuwajima, *J. Amer. Chem. Soc.*, 1970, **92**, 395.

³² G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Amer. Chem. Soc.*, 1972, **94**, 5106.

³³ S. S. Dua, A. E. Jukes, and H. Gilman, *Organometallic Chem. Synd.*, 1970/71, **1**, 87.

³⁴ I. Kuwajima and Y. Doi, *Tetrahedron Letters*, 1972, 1163.

³⁵ G. Köbrich, H. Trapp, and A. Akhtar, *Chem. Ber.*, 1968, **101**, 2644.

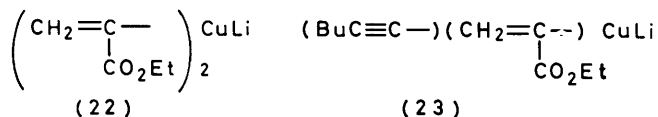
³⁶ H-L. Elbe and G. Köbrich, *Tetrahedron Letters*, 1974, 2557.

³⁷ K. Matsuzaki, T. Uryu, and K. Ito, *Makromol. Chem.*, 1969, **126**, 292.

³⁸ J. Klein and R. Levene, *J. Amer. Chem. Soc.*, 1972, **94**, 2520.

necessary³⁹ in coupling reactions resulted in this project being discontinued. However, Marino *et al.*⁴⁰ have prepared lithium α -ethoxycarbonylvinyl(hex-1-ynyl)cuprate (23), in which it was presumed that the acetylenic ligand, with its π -electron cloud, was co-ordinated to the copper metal with a stronger affinity than the ethoxycarbonylvinyl group, and that it remained as the residual moiety while the latter was transferred during a coupling reaction.

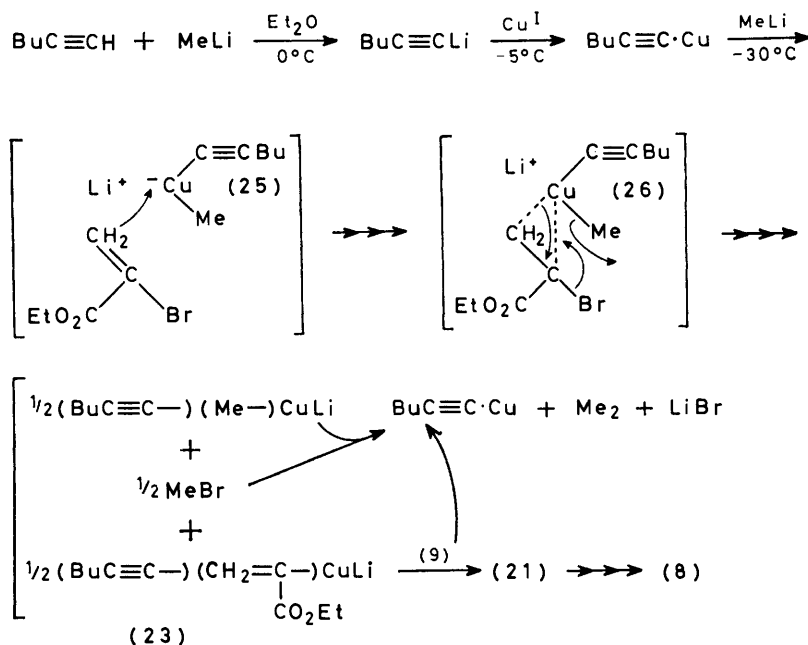
Before describing the use of the reagent (23),



we note that the mechanisms involved during organo-copper coupling have been discussed in the literature,^{28,30,31,38,41-45} and offer some further possibilities. According to Marino *et al.*⁴⁰ the preparation of (23)

α -bromoacrylate resulting in the intermediate (26). The introduction of this (higher) negative species could, in effect, constitute a nucleophilic substitution at copper with expulsion of the methyl group, which could then react with the partial positive bromide in a concerted reaction to release methyl bromide (0.5 equiv.), the cuprate (23) (0.5 equiv.), and starting material (25) (0.5 equiv.). The liberated methyl bromide, being inert to (23),⁴⁰ would react with the more nucleophilic, but less tightly bound, methyl group of (25), producing hex-1-ynylcopper, ethane, and lithium bromide. The combined elimination of the bromine cation and the alkyl group along with the participation of six electrons in the concerted reaction would ensure retention of configuration.

The cuprate (23) was successfully synthesised and 0.4 equiv. of (9; R = Et, R' = SiMe₃) were added to give the desired coupled product (21), which on hydrolysis yielded the diacid (8) in 75% yield.



SCHEME 8

involved the reaction of 0.5 equiv. of ethyl 2-bromoacrylate with the methylcuprate (25) (Scheme 8). To explain this we reason that, as with other oxidative addition-reductive elimination mechanisms,^{46,47} a *d* orbital of the copper metal in (25) co-ordinates with the π -electrons of the carbon-carbon double bond in the

Initial problems of non-reproducibility were related to the loss of methyl-lithium⁴⁸⁻⁵¹ at -30°C ; indeed it was found, by titration at this temperature, that the concentration of the alkyl-lithium was reduced by one-third. Apart from a footnote by Marino *et al.*,⁴⁰ who gave no details, nowhere had such a phenomenon been reported.

⁴⁶ M. Tamura and J. Kochi, *J. Amer. Chem. Soc.*, 1971, **93**, 1487.

⁴⁷ R. G. Pearson and W. R. Muir, *J. Amer. Chem. Soc.*, 1970, **92**, 5519.

⁴⁸ T. L. Brown, L. M. Seitz, and B. Y. Kimura, *J. Amer. Chem. Soc.*, 1968, **90**, 3245.

⁴⁹ H. L. Lewis and T. L. Brown, *J. Amer. Chem. Soc.*, 1970, **92**, 4664.

⁵⁰ L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *J. Amer. Chem. Soc.*, 1969, **91**, 1057.

⁵¹ L. M. Seitz and T. L. Brown, *J. Amer. Chem. Soc.*, 1966, **88**, 2174.

³⁹ G. H. Posner, *Org. Reactions*, 1975, **22**, 253.

⁴⁰ J. P. Marino and D. M. Floyd, *J. Amer. Chem. Soc.*, 1974, **96**, 7138.

⁴¹ H. O. House and M. J. Umen, *J. Amer. Chem. Soc.*, 1972, **94**, 5495.

⁴² R. W. Herr, D. M. Wieland, and C. R. Johnson, *J. Amer. Chem. Soc.*, 1970, **92**, 3813.

⁴³ J. K. Kochi and F. F. Rust, *J. Amer. Chem. Soc.*, 1961, **83**, 2017.

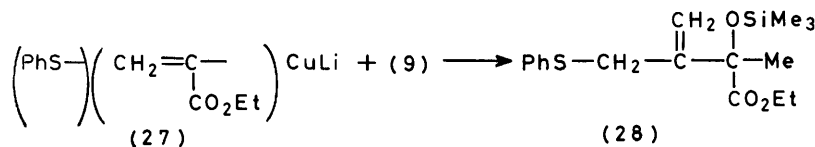
⁴⁴ R. G. Pearson, *Accounts Chem. Res.*, 1971, **4**, 152.

⁴⁵ H. O. House, *Accounts Chem. Res.*, 1976, **9**, 59.

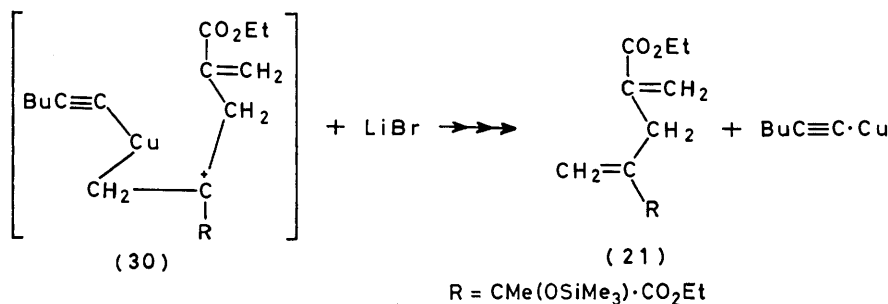
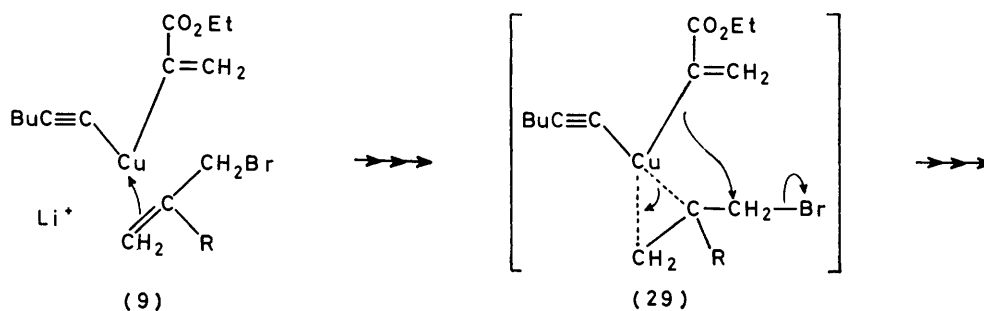
The decrease in concentration may be due to the formation of the cross-associated species $\text{Me}_3\text{Li}_4\text{Br}$ ⁵²⁻⁵⁴ in diethyl ether at low temperatures.

A further cuprate was also studied. Posner *et al.*⁵⁵ synthesised several cuprates in which the group to be retained was alkoxy, aryloxy, alkylthio, arylthio, or dialkylamino; of these five $(\text{PhS})(\text{R}^t)\text{CuLi}$ was found to be the most effective for allowing selective transfer

somewhat electrophilic. The specificity of (23) for allylic halides may result from the copper atom seeking additional electron density which could be satisfied by co-ordination of the halide through its olefinic group. This co-ordination, as illustrated by (29) (Scheme 10), would increase electron donation from the copper to the vinylic ligand, which would then be less tightly bound than the acetylenic ligand. This would enhance the



SCHEME 9



SCHEME 10

of the group R^t . However, in our hands the reaction of (9; R = Et, $\text{R}' = \text{SiMe}_3$) with the cuprate (27) (Scheme 9), prepared in an analogous fashion to (23), resulted in transfer of the phenylthio-group to produce (28).

Finally we propose a mechanism for the coupling reaction between the cuprate (23) and the ester (9; R = Et, $\text{R}' = \text{SiMe}_3$). Marino *et al.*⁴⁰ established that (23), although inert to simple alkyl halides, was reactive to activated allylic halides. He attributed this to the combined inductive effects of the acetylenic and ethoxycarbonylvinyl ligands. We argue that these groups, the acetylenic ligand in particular might be expected to be tightly bound to the copper through $\pi^*-\beta$ or $\pi^*-\delta$ orbital overlap and as a consequence the copper metal would be

negative character of the α -carbon atom of the ethoxycarbonylvinyl moiety, thus enabling it to couple with (9) to give (29), then (30), and finally (21).

Work is in progress on the resolution of (8) and its elaboration into swazincic acid dilactone (6).

EXPERIMENTAL

All glassware, used in organometallic reactions, was thoroughly cleaned and dried at 120 °C. Apparatus was assembled at this temperature and allowed to cool under a stream of nitrogen.

Nitrogen was pre-purified by passage through successive towers of molecular sieves (4 Å) and 'Carbosorb'.

Diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane,
⁵⁴ D. P. Novak and T. L. Brown, *J. Amer. Chem. Soc.*, 1972, **94**, 3793.

⁵⁵ G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Amer. Chem. Soc.*, 1973, **95**, 7788.

⁵² T. V. Talaleeva and K. A. Kocheshkov, *Izvest. Akad. Nauk. S.S.S.R., Ser khim.*, 1953, 126.

⁵³ T. L. Brown, *Pure Appl. Chem.*, 1970, **23**, 447.

and hexane were refluxed for several hours over calcium hydride then distilled under nitrogen, from lithium aluminium hydride, just prior to use.

All solvents and air-sensitive materials were transferred by hypodermic syringes or hypodermic tubing according to known methods.⁵⁶

Solutions of butyl- and methyl-lithium were standardised at room temperature (20 °C) according to the procedure of Watson and Eastham, using 2,2-bipyridyl as indicator.⁵⁷ In the case of methyl-lithium a further standardisation was performed at -30 °C.

Copper(I) iodide was continuously extracted with tetrahydrofuran in a Soxhlet apparatus (48 h) and dried, *in vacuo*, over sulphuric acid at 20 °C. (No advantage was forthcoming by using the techniques for purification of copper salts involving aqueous potassium halide solutions.⁵⁸)

All reactions involving organocopper compounds were performed in a four-necked cylindrical flask equipped with serum stoppers, all-glass magnetic stirrer, nitrogen inlet and outlet, and an adaptor for the addition of solids (where necessary). Prior to the introduction of solvents the apparatus, charged with copper(I) iodide, was flamed while being evacuated and then allowed to cool under a stream of nitrogen.

Sodium hydride (80% dispersion in oil) was washed free of oil with small portions of dry hexane and the supernatant hexane layer was removed by pipette.

Di-isopropylamine was distilled from calcium hydride (b.p. 84 °C) and stored over molecular sieves (4 Å) under nitrogen.

Hex-1-yne was distilled (b.p. 70–71 °C) under nitrogen and stored over molecular sieves (4 Å) at 0 °C. In the preparation of hex-1-ynyl-lithium sufficient ether (5–10 ml mmol⁻¹) was used to maintain total solution.

Ethyl 2,3-Epoxy-2,3-dimethylbutanoate (12).—Di-isopropylamine (4.24 ml, 30 mmol), followed by hexane (25.0 ml), was transferred into a flask fitted with a serum stopper and purged with nitrogen. The mixture was stirred and cooled to 0 °C, and butyl-lithium (10.7 ml; 2.8M-solution in hexane) was added *via* syringe. The mixture was cooled to -78 °C and tetrahydrofuran (20.0 ml) was added, followed by ethyl 2-bromopropionate (3.9 ml, 30 mmol). The red-orange enolate solution was stirred at this temperature for 0.5 h, acetone (2.2 ml, 30 mmol) in tetrahydrofuran (10.0 ml) was added, and stirring was continued for a further 1 h. The mixture was quenched with saturated aqueous ammonium chloride and extracted into ether; the extract was washed with sodium chloride solution, dried, evaporated, and distilled [b.p. 40° at 0.35 mmHg (lit.,⁵⁹ 83–87° at 25 Torr)]; yield 4.2 g (90%), δ (60 MHz; neat) 4.2 (2 H, q, O·CH₂·CH₃), 1.43 [6 H, s, (CH₃)₂C], 1.28 [3 H, s, OC·C(CH₃)₂·O], and 1.2 (3 H, t, O·CH₂·CH₃) (Found: C, 60.7; H, 8.9. Calc. for C₈H₁₄O₃: C, 60.7; H, 8.9%).

Ethyl 2-Hydroxy-2,3-dimethylbut-3-enoate (11; R = H).—Ethyl 2,3-epoxy-2,3-dimethylbutanoate (3.16 g, 20 mmol) in dry benzene (15.0 ml) was dropped on to a stirred suspension of lithium perchlorate (500 mg) in benzene (20.0 ml) in a water-bath at 25 °C. The mixture was stirred for 0.5 h at this temperature then refluxed for 18 h, cooled,

poured on to water, and extracted into ether. The organic layer was washed successively with hydrochloric acid (5%) and water, dried, evaporated, and distilled to give the product, b.p. 52° at 0.3 mmHg (2.85 g, 90%), δ (60 MHz; neat) 5.15 and 4.88 (2 H, 2s, C=CH₂), 4.2 (2 H, q, O·CH₂·CH₃), 3.84 (1 H, s, OH), 1.78 (3 H, s, CH₃C=), 1.5 (3 H, s, CH₃·C·O), and 1.2 (3 H, t, O·CH₂·CH₃) (Found: C, 60.7; H, 9.0. C₈H₁₄O₃ requires C, 60.7; H, 8.9%).

2-Hydroxy-2,3-dimethylbut-3-enoic Acid (13).—The ester (11; R = H) (1.0 g) was stirred (18 h) with aqueous 2N-sodium hydroxide (100 ml) at 20 °C. The solution was extracted with ether (extract discarded), acidified, and extracted continuously with ether; this extract was dried and evaporated to afford a solid. Crystallisation from cyclohexane gave the product, m.p. 86–87° (lit.,⁶ 87–88°), δ (60 MHz; CHCl₃) 6.5 (2 H, s, OH and COOH), 5.2 and 5.0 (2 H, 2s, C=CH₂), 1.8 (3 H, s, CH₃·C=), and 1.58 (3 H, s, CH₃·C·O) (Found: C, 55.2; H, 7.8. Calc. for C₆H₁₀O₃: C, 55.4; H, 7.7%).

Ethyl 2-Ethoxycarbonyloxy-2,3-dimethylbut-3-enoate (11; R = CO₂Et).—The ester (11; R = H) (8.7 g, 55 mmol) dissolved in dry 1,2-dimethoxyethane (50.0 ml) was added dropwise to a suspension of sodium hydride (1.65 g, 55 mmol; 80% dispersion in oil) in dry 1,2-dimethoxyethane (50 ml) at 20 °C. The mixture was stirred until evolution of hydrogen had ceased (2 h). Ethyl chloroformate (6.48 g, 60 mmol) dissolved in 1,2-dimethoxyethane (50 ml) was added dropwise, and the mixture, after stirring at 20 °C (3 h), was poured on to water, acidified, and extracted into ether. The organic layer was washed with water, dried, evaporated, and distilled; b.p. 58–60° at 1.0 mmHg; yield 9.5 g (75%), δ (60 MHz; neat) 5.15 and 4.98 (2 H, 2s, C=CH₂), 4.15 (4 H, q, O·CH₂·CH₃), 1.8 (3 H, s, CH₃·C=), 1.7 (3 H, s, CH₃·C·O), 1.3 (3 H, t, O·CO·CH₂·CH₃), and 1.2 (3 H, t, O·CH₂·CH₃) (Found: C, 57.2; H, 7.8. C₁₁H₁₈O₆ requires C, 57.4; H, 7.8%).

Ethyl 2,3-Dimethyl-2-trimethylsilyloxybut-3-enoate (11; R = SiMe₃).—Obtained as described above using trimethylsilyl chloride as the electrophile, this had b.p. 65–68° at 1.0 mmHg (yield 85%) (Found: C, 58.0; H, 9.4. C₁₁H₂₂O₃Si requires C, 57.9; H, 9.6%).

Ethyl 3-Bromomethyl-2-hydroxy-2-methylbut-3-enoate (9; R = Et; R' = H).—The ester (11; R = H) (7.9 g, 50 mmol) was refluxed (2 h) in carbon tetrachloride (150 ml) with *N*-bromosuccinimide (9.75 g, 55 mmol) in bright sunlight. The mixture was cooled, the succinimide filtered off at 0 °C, and the residue chromatographed on silica gel with benzene. Evaporation of the eluate afforded an oil (11.26 g, 95%), δ (60 MHz; CCl₄) 5.55 (2 H, s, C=CH₂), 4.25 (2 H, q, O·CH₂·CH₃), 4.20 (2 H, s, C=CH₂Br), 4.1 (1 H, s, OH), 1.6 (3 H, s, CH₃·C·O), and 1.3 (3 H, t, O·CH₂·CH₃).

Ethyl 3-Bromomethyl-2-ethoxycarbonyloxy-2-methylbut-3-enoate (9; R = Et, R' = CO₂Et).—This was obtained as above from ethyl 2-ethoxycarbonyloxy-2,3-dimethylbut-3-enoate; yield 14.4 g (93%), δ (60 MHz; CCl₄) 5.58 (2 H, s, C=CH₂), 4.18 (4 H, q, O·CH₂·CH₃), 4.10 (2 H, s, CH₂Br), 1.8 (3 H, s, CH₃·C·O), 1.3 (3 H, t, O·CO·O·CH₂·CH₃), and 1.25 (3 H, t, O·CH₂·CH₃).

Ethyl 3-Bromomethyl-2-methyl-2-trimethylsilyloxybut-3-enoate (9; R = Et, R' = SiMe₃).—This was obtained as above from using ethyl 2,3-dimethyl-2-trimethylsilyloxybut-3-enoate; yield 14.4 g (93%).

⁵⁶ D. F. Shriver, 'The Manipulation of Air-sensitive Compounds,' McGraw-Hill, London, 1969.

⁵⁷ S. C. Watson and J. F. Eastham, *J. Organometallic Chem.*, 1967, **9**, 165.

⁵⁸ G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, 1963, **7**, 9.

⁵⁹ A. Oku, M. Okano, T. Shono, and R. Oda, *Kogyo Kagaku Zasshi*, 1965, **68**, 821.

Triethyl 4-Ethoxycarbonyloxy-3-methylene-pentane-1,1,4-tricarboxylate (18; R = CO₂Et). Diethyl malonate (1.6 g, 10.0 mmol) in dry tetrahydrofuran (15.0 ml) was dropped slowly on a stirred suspension of sodium hydride (300 mg, 10.0 mmol; 80% dispersion) in tetrahydrofuran (50.0 ml), and the mixture was stirred until homogeneous (0.5 h). Ethyl 3-bromomethyl-2-ethoxycarbonyloxy-2-methylbut-3-enoate (3.1 g, 10.0 mmol) in tetrahydrofuran (15.0 ml) was added dropwise and the mixture was refluxed (4 h), cooled, quenched with water, and extracted into ether. The organic layer was dried and evaporated to afford an oil (2.8 g, 75%), pure by t.l.c. (8.5:1.5 benzene-acetic acid), δ (60 MHz; CCl₄) 5.28 and 5.0 (2 H, 2s, C=CH₂), 4.2 (8 H, q, O·CH₂·CH₃), 3.6 (1 H, t, CH·CH₂), 2.7 (2 H, d, CH·CH₂), 1.75 (3 H, s, CH₃·C), and 1.3 (12 H, m, O·CH₂·CH₃).

2-Hydroxy-2-methyl-3,5-dimethylenehexanedioic Acid (8) via the *Tricarboxylate* (18).—The foregoing material was hydrolysed with 6*N*-sodium hydroxide at 20 °C (24 h) and the basic solution extracted with ether (extract discarded), acidified, and re-extracted to afford, after drying and removal of solvents, a viscous oil. T.l.c. (silica gel; 9:1 ethyl acetate-acetic acid) afforded the triacid (19) (95%), which resisted crystallisation.

The triacid (1.62 g, 70 mmol) was dissolved in a Mannich reagent stock solution (7.0 ml) prepared from glacial acetic acid (40 ml), aqueous formaldehyde (30 ml), diethylamine (10.0 ml), and sodium acetate (1.1 g). The mixture was stirred at 20 °C (1 h) then heated on a steam-bath (2 h), cooled, basified, and extracted with ether (extract discarded). The aqueous layer was acidified and continuously extracted into ether; the organic layer was dried and evaporated to afford a crystalline solid. Recrystallisation [ethyl acetate-light petroleum (b.p. 60–80 °C)] afforded the pure *acid* (8), m.p. 120–121° (900 mg, 70%), δ (60 MHz; CDCl₃) 6.4 and 5.75 (2 H, 2s, CH₂=C=C=O), 5.4 and 5.0 (2 H, 2s, C=CH₂), 3.15 (2 H, s, CH₂·C=), and 1.6 (3 H, s, CH₃·C·O) (Found: C, 54.3; H, 6.4. C₉H₁₂O₅ requires C, 54.0; H, 6.0%).

Ethyl 2-Bromoacrylate (20; R = Br).—Bromine (40.0 g, 250 mmol) was added dropwise to a stirred solution of ethyl acrylate (25.0 g, 250 mmol) in carbon tetrachloride (100 ml). The mixture was then stirred for 1 h and evaporated to afford ethyl 2,3-dibromopropionate as a crude oil. This (62.4 g, 240 mmol) was treated with quinoline (39.0 g, 300 mmol) and hydroquinone (5.0 g) at

100 °C (0.25 h), then the product was distilled into a receiver containing hydroquinone; b.p. 60° at 20 mmHg (lit.⁶⁰ 55–58° at 12 mmHg); yield 32.0 g (75%).

The Hexanedioic Acid (8) via the *Cuprate* (23).—Hex-1-yne (1.14 ml, 10.0 mmol), followed by ether (60 ml), was transferred, under nitrogen, to a flask equipped with stirrer, serum stopper, and a static source of pre-purified nitrogen. The mixture was cooled to 5 °C and methyl-lithium (4.8 ml; 2.09*M* in ether) was added. The solution was stirred until evolution of gas ceased (0.25 h) and then quantitatively transferred, under nitrogen, to a slurry of copper(I) iodide (1.9 g, 10.0 mmol) in ether (60.0 ml), held at 0–5 °C in a second four-necked flame-dried flask also equipped with stirrer, serum stopper, and nitrogen inlet and outlet.

The yellow suspension of hex-1-ynylcopper was stirred at ±10 °C (1 h) then cooled to –30 °C, and a second equivalent of methyl-lithium (7.2 ml; 1.39*M*) was added to produce a homogeneous solution. This solution of lithium hexyn-1-yl(methyl)cuprate, after stirring at –30 °C (0.5 h) was cooled to –78 °C, and ethyl 2-bromoacrylate (0.61 ml, 5.0 mmol), freshly distilled from the stock solution and dissolved in ether (10.0 ml), was added. The mixture was stirred at –78 °C (1 h), and ethyl 3-bromomethyl-2-methyl-2-trimethylsilyloxybut-3-enoate (0.78 ml, 4.0 mmol) dissolved in ether (15.0 ml) was added. The mixture was stirred at –78 °C (18 h), quenched with saturated ammonium chloride, filtered through Celite, and extracted with ether. The organic layer was dried and evaporated to afford an oil, pure by t.l.c. (9:1 benzene-acetic acid) (1.1 g, 85%), δ (60 MHz; CHCl₃) 6.15 and 5.5 (2 H, 2s, CH₂=C=C=O), 5.15 and 4.9 (2 H, 2s, C=CH₂), 4.15 (4 H, q, O·CH₂·CH₃), 3.1 (2 H, s, CH₂·C=), 1.5 (3 H, s, CH₃·C·O), 1.3 (3 H, t, O·CH₂·CH₃), and 0.23 [9 H, s, OSi(CH₃)₃].

This material was hydrolysed with 6*N*-sodium hydroxide at 20 °C (24 h); the basic solution was extracted with ether (extract discarded), acidified, and re-extracted to afford, after drying and removal of solvents, a crystalline solid. Recrystallisation [ethyl acetate-light petroleum (b.p. 60–80 °C)] afforded the acid (8), m.p. 120–121°, identical with that described above.

We thank the South African Council for Scientific and Industrial Research for grants, and Professor J. P. Marino, Michigan State University, for assistance concerning experimental detail.

⁶⁰ C. S. Marvel, J. Dec, H. G. Cooke, jun., and J. C. Cowan, *J. Amer. Chem. Soc.*, 1940, **62** 3495.